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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/772,272	02/06/2004	Misa Tominaga	US-108	4146

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FORD, VANESSA L	
ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/772,272	TOMINAGA ET AL.	
	Examiner	Art Unit	
	Vanessa L. Ford	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7 and 9-12* is/are pending in the application.

4a) Of the above claim(s) *9-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 7, 2007 has been entered. The response to the Final Office action was filed May 22, 2007. Claims 2-3 and 8 have been canceled. Claims 9-12 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1 and 4-7 are under examination. The declaration submitted by Takayuki Asahara filed May 22, 2007 under 37 C.F.R. 1.132. However, the declaration is insufficient to overcome the rejections of record.

Rejections Withdrawn

2. In view of Applicant's amendment and response the following rejections are withdrawn:

a) rejection of claim 1 under 35 U.S.C. 112 second paragraph, page 5, paragraph 5 is withdrawn.

b) rejection of claim 1 under 35 U.S.C. 112 second paragraph, page 6, paragraph 6 is withdrawn

Rejection Maintained

3. The rejection under 35 U.S.C. 112, first paragraph is maintained for claims 1 and 4-7 for the reasons set forth on pages 3-5 paragraph 4 of the Final Office Action.

The rejection is reiterated below:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The claims are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a *Bacillus* bacterium which is modified so that growth inhibition by 6-ethoxypurine is reduced and has inosine-producing ability.

The claims broadly encompass a genus of *Bacillus* mutants. There is substantial variability among the species of *Bacillus* mutants encompassed within the scope of the claims. The instant specification teaches that *Bacillus* mutants of the invention can be made by mutagenesis treatment with UV irradiation or treatment with mutagenizing agent used for typical mutagenesis treatment such as N-methyl-N'-nitro-N-nitrosoguanidine (NTG) and nitrous acid (page 13). The specification teaches that mutations may be made by disruption of the "normal gene" with a "disrupted-type purR gene" (pages 8-9). The instant specification teaches that the disrupted-type purR gene can be obtained by specifically using deletion of a certain region of the purR gene using digestion with restriction enzyme and re-ligation, insertion of another DNA fragment (marker gene etc.) into the purR gene (site-directed mutagenesis). The specification does not place any structure limitations on the *Bacillus* mutants. The instant specification does not teach what locations in the purR gene are mutated to arrive at the claimed *Bacillus* bacterium. The scope of the claims include numerous structural variants and the genus is highly variant because a significant number of structural difference between genus members is permitted. Structural features that could distinguish compounds in the genus from others in the gene class are missing from the disclosure and the claims. No common structural attributes identify the members of the genus. There is no guidance provided as to which nucleic acids can be deleted or

substituted and the encode polypeptide still has its biological function. Since the purR nucleic acid sequence encodes a protein, the prior art below teaches the difficulties associated with amino acid modification within a protein.

Thomas E. Creighton, in his book, "Proteins: Structures and Molecular Properties, 1984", (pages 314-315) teaches that variation of the primary structure of a protein can result in an instable molecule. He teaches that a single amino acid change can cause a mutant hemoglobin to have lower stabilities due to any of several causes: 1) alteration of close-packing of the interior; loss of one group that normally participates in a hydrogen bond or salt bridge; 2) the introduction of a charged or polar group into the interior or the insertion into a helical region of a proline residue, which must distort the alpha-helix; 3) while sometimes radical changes of surface groups, even introduction of a non-polar side chain have no great effect on stability.

Thomas E. Creighton, in his book "*Protein Structure: A Practical Approach, 1989; pages 184-186"* teaches that present day site directed mutagenesis of a gene allows any amino acids in a protein sequence to be changed to any other, as well as introducing deletions and insertions". The reference goes on to teach that it is difficult to know which amino acid to change and which is the best residue to substitute for the desired functional and structural effect.

Nosoh, Y. et al in *"Protein Stability and Stabilization through Protein Engineering, 1991" (chapter 7, page 197, second paragraph)* adds support to Thomas E. Creighton, by teaching that results so far accumulated on the stability and stabilization of proteins appear to indicate that the strategy for stabilizing proteins differ from protein to protein and that any generalized mechanisms for protein stability have not yet been presented. The mere recitation of a "...which is deficient in one or more genes negatively acting on the biosynthesis of inosine or involved in degradation of inosine and selected from a purine operon repressor gene, succinyl-AMP synthase gene and purine nucleoside phosphorylase gene" does not provide a structure for the claimed *Bacillus* mutants. One skilled in the art would not recognize from the claimed disclosure that the applicant has taught how to make and use the claimed *Bacillus* mutants. What position within the purR gene or other genes can be modified to arrive at the claimed bacterium? The specification does not enable numerous *Bacillus* mutants encompassed by the claimed invention.

To address the newly amended claim 1, the instant specification lacks written description for the newly added claim limitation, "wherein said bacterium is further modified to be less susceptible to growth inhibition by 6-ethoxypurine in the presence of 2000 mg/L of 6-ethoxypurine as compared to a *Bacillus subtilis* strain having the same gene disruption as said inosine-producing *Bacillus* bacterium". The instant specification has failed to teach or disclose where this limitation is specifically shown or implied.

Therefore, Applicant have not met the enablement requirements as set forth in U.S.C. 112, first paragraph.

Applicant's Arguments

Applicant urges that the claims have been amended to specifically define the Bacillus mutant in that the deficiencies in the genes are specifically recited. Applicant urges that the gene(s) are disrupted and method for disrupting the genes are well-described in the specification. Applicant urges that these genes are well known and so are their structures and since the goal is to disrupt these genes so that expression is inhibited, the comments directed to maintenance or stability do not apply. Applicant urges that it does not require much skill or prediction insight to disrupt a gene so that it does not function. Applicant urges that the specification is completely enabling for the claimed invention.

Examiner's Response to Applicant's Arguments

Applicant's arguments filed July 7, 2007 have been fully considered but they are not persuasive. . It is the Examiner's position that the specification has not enabled the claimed invention because specification fails to disclose where the modifications are made within the gene(s) (e.g. purR, purA or deoD or combinations thereof) to arrive at a bacterium that is an inosine-producing bacterium and is further modified to be is less susceptible to growth inhibition by 6-ethoxypurine in the presence of 6-ethoxypurine as compared to a bacterium having the same gene disruption as said inosine-producing bacterium. Although it is well within the skill in the art to modify genes or proteins, the instant specification does not provide the guidance necessary for one of skill in the art to obtain an inosine producing bacterium since the art is unpredictable regarding gene

and/or protein modification. The instant specification has not provide any guidance as to where (at what location) the "purR gene", purA gene or deoD gene are modified to result in an inosine producing bacterium. Without this guidance experimentation is undue.

In view of all of the above, this rejection is maintained since Applicant has not met their burden under 35 U.S.C. 112, first paragraph.

4. The rejection under 35 U.S.C. 102(b) is maintained for claims 1 and 4-7 for the reasons set forth on pages 6-8 paragraph 7 of the Final Office Action.

The rejection is reiterated below:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 3-7 are rejected under 35 U.S.C. 102(b) as anticipated by Sato et al *(U. S. Patent No. 6,284, 495 B1 published September 4, 2001)*.

Claims 1 and 3-7 are drawn to an isolated inosine-producing *Bacillus* bacterium which has reduced growth inhibition by 6-ethoxypurine as compared to Bacillus 168 Marburg strain wherein said bacterium is deficient in a gene selected from the group consisting of the purR gene, the purA gene, the deoD gene and combinations thereof.

Sato et al teach a bacterium that has been disrupted in the purR gene (see the Abstract and column 4). Sato et al teach that the bacterium of the invention was a Bacillus subtilis 168 Marburg strain (column 4). Sato et al teach that the bacterium can be used to produce nucleic acid substances including "inosinic acid". Therefore, the art teaches the claim limitation "inosine producing". Claims limitations such as " ...wherein said reduced growth inhibition occurs in the presence of 2000 mg/L ethoxypurine" and "...wherein said reduced growth inhibition occurs on solid medium" would be inherent in bacterium of the prior art. Claims limitations such as "wherein the medium has an ethoxypurine content of 2000 mg/L", "wherein the bacterium is cultured on a solid medium containing 6-ethoxypurine and a solid medium not containing 6-ethoxypurine, the bacterium shows a relative growth degree of 80 or more which is defined by the

following equation: Relative growth degree (%) =[colony diameter (mm) observed in the medium containing 6-ethoxypurine]/[colony diameter (mm) observed in the medium not containing 6-ethoxypurine] x 100", "wherein the solid medium containing 6-ethoxypurine comprises 6-ethoxypurine content of 2000 mg/l.", "wherein the solid medium is a minimal medium" and "which is deficient in one or more genes negatively acting on the biosynthesis of inosine or involved in degradation of inosine and selected form a purine operon repressor gene, succinyl-AMP synthase gene and purine nucleoside phosphorylase gene" are being viewed as process limitations. It should be noted that the products of the prior art reference appear to be the same or an obvious or analogous variant of the product claimed by the applicant because they appear to possess the same or similar functional characteristics. The purification or production of a product by a particular process does not impart novelty or unobviousness to a product when the same product is taught by the prior art. This is particularly true when properties of the product are not changed by the process in an unexpected manner. See In re Thorpe, 227 USPO 964 (CAFC 1985); In re Marosi, 218 USPO 289, 29222-293 (CAFC 1983); In re Brown, 173 USPO 685 (CCPA 1972). Even if applicant's product can be shown to be of higher purity than the product of the prior art reference, applicant's needs to show some unexpected and unique utility or property, such as unexpected biologically significant increase in specific activity with which the increased purity, greater stability and/or practicality or freedom from some restrictive element or adverse side effects inherent in the product preparations of the prior art or some other secondary consideration which the additional degree of purity imparts (to which there is a basis in the specification) to applicant's product in order to overcome the aspect of the product's purity is relied upon.

Since the Office does not have the facilities for examining and comparing applicant's bacterium with the bacterium of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the bacterium of the prior art does not possess the same material structural and functional characteristics of the claimed bacterium). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Applicant's Arguments

Applicant urges that claim 1 has been amended to recite that the bacterium is further modified to be less susceptible to growth inhibition by 6-ethoxypurine in the presence of 2000 mg/L of 6-ethoxypurine. Applicant urges that Sato et al does not teach this feature either explicitly or inherently.

Applicant urges that the declaration under 37 C.F.R. 1.132 presenting original data which shows that the resistance to 6-ethoxypurine is not inherent in a purR disrupted strain such as Sato et al, but is specifically imparted by a mutagenesis technique such as those described in the Example 2 of the specification. Applicant urges that this data shows that the purR disrupted strain disclosed in Sato et al is not resistant to 6-ethoxypurine and therefore, cannot be anticipatory of the present invention.

Examiner's Response to Applicant's Argument

It is the Examiner's position that the declaration under 37 C.F.R. 1.132 is insufficient to overcome the rejection. As states by Applicant, the claims have been amended to recite that the bacterium is further modified to be less susceptible to growth inhibition by 6-ethoxypurine in the presence of 2000 mg/L of 6-ethoxypurine. However, the instant specification has not taught or disclosed the "further modification" that is made to the claimed bacterium. The declaration under 37 C.F.R. 1.132 merely shows that the bacterium with a disrupted purR gene used in the experiments disclosed in the declaration is not resistant to 6-ethoxypurine. However, this rejection is maintained because Applicant has not shown that the disruption of the purR gene of *Bacillus* bacterium as taught by Sato et al differs from the purR gene disruption of the claimed invention. Thus, this rejection is maintained.

New Grounds of Rejection Necessitated by Amendment

New Grounds of Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1 and 4-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *This is a new matter rejection.* The amendment filed May 22, 2007 introduces new matter into the claims.

The claims have been amended to recite, " wherein said bacterium is further modified to be less susceptible to growth inhibition by 6-ethoxypurine in the presence of 2000 mg/L of 6-ethoxypurine as compared to a *Bacillus subtilis* strain having the same gene disruption as said inosine-producing *Bacillus* bacterium". 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention.

Applicant's amendment introduces "new matter" that is not supported by the original disclosure. The specification fails to disclose the newly added claim limitation. Applicant directs the Examiner to paragraphs [0062-0065] of the instant specification. The Examiner has reviewed the instant specification and has failed to find where

support for this amendment is specifically shown or implied. Applicant is required to cancel the new matter in the reply to this Office Action.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 1 is rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites "less susceptible". It is unclear as to what Applicant intends. The recitation of this phrase does not define a level or a degree of susceptibility. Correction and/or clarification is required.

7. Claim 1 is rejected under 35 USC 112 second paragraph for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites "wherein said bacterium is further modified.". It is unclear as to what further modification Applicant intends. Correction and/or clarification is required.

Status of Claims

8. No claims are allowed.

Conclusion

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vanessa L. Ford whose telephone number is (571) 272-0857. The examiner can normally be reached on 9 am- 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Vanessa L. Ford
Biotechnology Patent Examiner
September 10, 2007

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